UNITED STATES DEPARTMENT OF COMMERCE
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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/652,978	02/08/91	BUHR	C 4610-0027

KUNZ, EXAMINER

18M2/1116

ART UNIT	PAPER NUMBER
1803	31

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DATE MAILED: 11/16/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8-10-95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 51-54 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 51-54 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

07/652,978

PTOL-326 (Rev. 2/93)

EXAMINER'S ACTION

Applicant's amendment D and information disclosure statement filed August 10, 1995 have been received and entered into the record.

Claims 51 - 54 are pending in the case. All non-elected claims have been canceled.

Any 35 USC statutes not cited in this Office action can be found cited in full in a previous Office action.

The previous rejection of claims 7, 10, and 27 (now canceled) under 35 USC 103 as being obvious over Borthwick et al. in view of Reist et al. has been withdrawn because the filing date of the instant application, February 2, 1991, predates the publication date of the Borthwick et al. reference, March, 1991.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 53 and 54 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Martin et al. (CA 109: 231447m).

The claims are directed to guanosine 5'-methylenephosphonate. The Martin et al. reference discloses this very nucleoside analog as compound II.

However, the claims 51 and 52 are rejected under 35 USC 103 as being obvious over Chu et al. in view of Reist et al. for the

reasons already of record on pages 2 - 3 of the Office action mailed February 8, 1995.

Claims 51 - 52 encompass 9-(2-deoxy-2-fluoro-B-D-arabino-furanosyl)guanine--5'-methylenephosphonate.

Chu et al. discloses the unphosphorylated nucleoside analog: 9-(2-deoxy-2-fluoro-B-D-arabinofuranosyl)guanine on page 338 as compound VI. Furthermore, Chu et al. indicates that compound VI exhibited considerable activity against human leukemic cells,, particularly the T cell line CCRF-CEM (page 337, column 2, lines 2 - 5; Table II on page 338).

While Chu et al. does not mention any 5'-methylenephospho-nates derivatives of 9-(2-deoxy-2-fluoro-B-D-arabinofuranosyl) guanine, Reist et al. does teach that 5'-methylenephosphonate derivatives of nucleoside analogs can circumvent cellular resistance by using instead, the 5'-methylenephosphonate derivative. The use of the 5'-methylenephosphonate derivative obviates the requirement for the initial enzymatic phosphorylation step (pages 1 - 2), regardless whether the compound is an antiviral or anticancer agent. Thus, the claimed compounds are prima facie obvious in the absence of clear and convincing evidence to the contrary. The applicant has presented no such evidence.

The applicants have argued against the obviousness rejections on the grounds that the Borthwick et al. reference is

not valid prior art. This argument has been fully considered and is deemed persuasive. Therefore, the obviousness based in part upon the Borthwick reference has been withdrawn.

The applicants have further argued that the Montgomery et al. (J. Med. Chem. 22: 109, 1979) teaches against the claimed 5'-methylenephosphonates because the 5'-methylenephosphomate derivative of 2'-deoxy-5-fluorouridylic acid did not yield a molecule with the same biological properties as the parent molecule. This argument has been fully considered but is not deemed persuasive. Montgomery et al. teaches that the 5'-methylenephosphonate derivative of 2'-deoxy-5-fluorouridylic acid inhibited the thymidylate synthetase as did the regular 5'-phosphate derivative except that the enzyme had to be preincubated with the compound. Furthermore, this 5'-methylene phosphonate derivative was moderately cytotoxic to neoplastic cells (page 110, column 1, third paragraph). Just because the 5-methylenephosphonate did not exhibit the identical anticancer profile as the 5'-phosphonate does not mean that it would not be an effective agent against cancer cells resistant to 2-deoxy-5-fluorouridine. The activity of the 5'-phosphonate derivative may well have greater activity against resistant tumors cells than the 5'-phosphate derivative.

The applicants further argue against this obviousness rejection on the grounds that Chu teaches away from the claimed invention as an anti-HSV-1 agent. Specifically, the applicant notes that Chu states on page 337, second column, paragraph bridging to page 338: "None of the new 2'-fluoro-ara-purines demonstrated significant antiviral activity against HSV-1." This argument has been fully considered but is not persuasive. The instant claims are directed to compounds per se, and not to a method of using said compounds to treating herpes infections. In order to establish a prima facie case of the examiner is not required to show that the prior art teaches that the claimed compounds possess anti-HSV-1 activity. Instead, the examiner must establish that the artisan would have been motivated to have modified the known compound, 9-(2-deoxy-2-fluoro-arabino-furanosyl)guanosine to yield the 5'-methylenephosphonate as taught by Reist et al. Clearly, Chu et al. teaches that the 2'-fluoro-araG possesses anticancer activity (page 337, column 2, lines 2 - 5). It is well known that the mode of action of most antiviral and/or anticancer nucleoside analogs requires that the nucleoside be phosphorylated. However, cells which become resistant to such drugs possess a diminished ability to phosphorylate nucleosides. Therefore, Reist et al. teaches that the use of the 5'-methylenephosphonate derivatives can aid the agent in crossing the cell membrane and in circumventing the

requirement to be monophosphorylated. In summary, the artisan would have known how to synthesize the claimed compounds and would also have been motivated to do so in order to increase the ability of the compound to penetrate the cell membrane and to obviate the necessity for enzymatically phosphorylation.

Lastly, the applicant argues that the effect of a modification of nucleosides is not predictable because the compounds are very sensitive to structural modifications. In addition, the applicant refers to the reference by Buhr et al. (some of the coinventors) as evidence that the claimed compounds inhibit herpes viruses and are quite sensitive to structural changes. This argument has been fully considered but is not deemed persuasive. The Buhr et al. reference shows that changes in the heterocyclic base and changes at the 2'-position of the ribose do create substantial differences in activities among the various 5'-methylenephosphonates. However, the change which the examiner refers to in this obviousness rejection is the modification of a nucleoside to a 5'-methylenephosphonate. Since nucleosides must become phosphorylated intracellularly in order to be effective, the exogenous addition of a stable phosphorus group, i.e. the 5'-methylenephosphonate, should also yield a biologically active agent. Buhr et al. is not convincing because it does not compare the activity

of a series of nucleoside analog and their respective 5'-methylenephosphonates.

Claims 51 - 54 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 51 and 53 are rendered vague and indefinite because the chemical structure contains no variable " R1 ", yet " R1 " is defined beneath the structure.

Claim 51 and 53 are further rendered vague and indefinite because the abbreviation "HTEA+" is not defined within the claim itself.

Claims 51 - 54 are rejected under 35 USC 112, first paragraph, because the specification fails to provide an adequate written description of the invention and fails to teach adequately how to make and/or use the invention, i.e., the disclosure is not enabling for the claimed subject matter, for the reasons already of record on page 2 of the Office action mailed February 8, 1995.

The applicant argues against this lack of enablement rejection on the grounds that the specification teaches that the claimed compounds are active against "herpes viruses" on page 6, lines 16 - 29. This argument has been fully considered but is

not deemed persuasive for the following reasons. Under 35 USC 112, first paragraph, the law requires that the applicant provide a written description of the invention "**in such full, clear, concise, and exact terms**" as to enable the artisan to make and use the invention. There are several types of herpes viruses, including herpes simplex type 1, herpes simplex type 2, varicella zoster (VZV), etc. Consequently, a general statement that the claims compounds are effective against herpes viruses without any antiviral data showing efficacy against a specific type of herpes viruses is deemed inadequate to satisfy the first paragraph of USC 112. Furthermore, applicant's own data (Buhr et al., Collect. Czech. Chem. Commun. 58 102 - 104, 1993) published two years after the filing date of the instant application shows that only 2'-deoxy-5'-methylenephosphonate guanosine derivatives (wherein 2'-position has a hydrogen or a fluorine atom) exhibited any antiviral activity against even a single type of herpes virus--varicella zoster. There is no inhibition found against herpes simplex types 1 and 2 (page 104, Table 1). Additionally, the instant claims encompass not just two specific compounds with guanine as the sole heterocyclic base, but also 5'-methylene-phosphonates wherein the base is 2,6-diaminopurine or N2-isobutyrylguanine. Given the fact that only two of the 7 5'-methylenephosphonates tested by applicants in their subsequent paper show any activity and then only against one type of herpes

virus, the person of ordinary skill in the art would certainly question the antiviral activity of a majority of the claimed compounds since applicant, himself, has established the high degree of **unpredictability** in the art of 5'-methylene-phosphonate nucleoside analogs. The applicant is not only claiming 5'-methylene phosphonates with varied heterocyclic bases without substantiating documentation, but also varied phosphonate moieties with R2 ranging from C1 to C12. Without additional **guidance** in the specification for using the claimed compounds as antiviral agents, there is clearly a **burden of undue experimentation** placed upon the artisan wanting to practice the invention. The law requires that the applicant teach the artisan how to make and use the invention--not how to find out how to use the invention (In re Gardner, 166 USPQ 138).

No claim is allowed.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE

STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kunz, whose telephone number is (703) 308-4623. The examiner can normally be reached on Tuesday through Friday from 6:30 AM to 4:00 PM. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Robinson, can be reached on (703) 308-2897. The fax phone number for this Group is (703) 305-3230.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Gary L. Kunz

GARY L. KUNZ
PATENT EXAMINER
GROUP 1800

Gary L. Kunz, Ph.D.
November 6, 1995